Journal of Breast Cancer
J Breast Cancer 2016 September; 19(3): 283-291 http://dx.doi.org/10.4048/jbc.2016.19.3.283

ORIGINAL ARTICLE

Increased Incidence of Breast Cancer in Postmenopausal Women with High Body Mass Index at the Modena Screening Program

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Purpose: We conducted a study to evaluate the relationship between body mass index (BMI) and the risk of breast cancer (BC) and outcome in a population of 14,684 women aged 55 to 69 years eligible to participate in the Mammography Screening Program (MSP) in the Province of Modena, Italy. **Methods:** The study population was drawn from women who underwent mammography screening between 2004 and 2006 in the Province of Modena. Women were subdivided into obese, overweight, and normal-weight categories according to BMI and followed until July 31, 2010, to evaluate the BC incidence. The clinicopathological characteristics of BC were also evaluated in different groups of patients classified according to BMI. After BC diagnosis, patients were followed for a median period of 65 (range, 2–104) months. Second events (recurrences and second tumors) were recorded, and the 5-year event-free survival (EFS) was calculated. **Results:** After a period of 73 months, 366 cases of BC were diagnosed. Compared with normal-weight women, obese women had a significantly higher incidence of BC (relative risk [RR], 1.32; $p=0.040$) (RR=1), larger tumors (27% of tumors were larger than T2 size), and more nodal involvement (38.5% of tumors were node-positive). Furthermore, a significantly higher rate of total events was seen in obese women compared with overweight and normal-weight patients, respectively (17.9% vs. 11.4% vs. 10.8%, $p=0.032$). The 5-year EFS was 89.0%, 89.0%, and 80.0% for normal-weight, overweight, and obese patients, respectively. **Conclusion:** We observed a significantly higher risk of BC in obese women among those eligible to participate in the MSP in the Province of Modena. Finally, obese women had more second events and poorer EFS compared to nono bese women.

Key Words: *Body mass index, Breast neoplasms, Mammography, Mass screening, Outcome assessment*

INTRODUCTION

Obesity is a well-recognized risk factor for breast cancer (BC) in postmenopausal women. Studies indicate that all measures of obesity, such as waist to hip ratio (WHR), weight gain, body mass index (BMI), and percent body fat, are associated with an increased risk of postmenopausal BC [1-4]. On the contrary, in premenopausal women, high body weight may be protective among women with fat accumulation in the lower body (low WHR) [5-7].

Obesity is also associated with a poorer prognosis and increased mortality for patients with BC, which probably results from a diagnostic delay that leads to more advanced disease stages. Furthermore, BC in these patients is more aggressive because obesity is associated with the upregulation of a number of cellular proliferation pathways and is directly related to circulating estrogen levels. Moreover, obese patients are more likely to receive reduced doses of chemotherapy compared with normal-weight women [8-11].

Obesity and BC may have a considerable negative impact on public health. In the United States, it is estimated that 20% of all BC cases and up to 50% of deaths due to BC in postmenopausal women can be attributed to obesity [12]. A prospective study performed on an Italian population assessed the risk of BC in obese women according to biohumoral parameters such as glycemic index and area under the glucose response curve [13], but to our knowledge, there are no data focusing on the relationship between anthropometric vari-

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Received: January 21, 2016 **Accepted:** June 18, 2016

http://ejbc.kr | pISSN 1738-6756
eISSN 2092-9900

ables and the risk of BC in the Italian population. Furthermore, it is widely accepted that BMI is positively associated with several types of cancers including tumors of the colon and endometrium, adenocarcinoma of the esophagus, and kidney cancer [14]. Therefore, we conducted a study to evaluate the relationship between BMI and BC incidence and outcome (including relapses and second tumors) in a population of more than 14,500 women aged 55 to 69 years in the Province of Modena, Italy.

METHODS

Study population

The Mammography Screening Program (MSP) was started in 1995 in the Municipality of Modena and gradually extended to other districts of the province, with a population of 701,500 inhabitants of which 358,134 are women.

Briefly, as established by the Italian National Health Service, all the asymptomatic women without palpable or clinical signs of breast lesions who were residents in the Province of Modena and aged 50 to 69 years were invited by letter to undergo a biannual bilateral two-view (i.e., lateral and oblique projections for right and left breast) screening mammogram. The screening mammogram was read by two radiologists; for suspicious findings, the patient was recalled for a second look, usually by ultrasound or by a focused radiogram, and a subsequent core or vacuum-assisted biopsy was performed to characterize the lesion. In case of suspected or definitively diagnosed carcinoma, the patient underwent breast surgery and the final histology results were sent to the screening program and registered in a regional database.

The first screening round started in October 1995 and ended in December 2001. Data on women invited to the MSP are registered and collected at the beginning and every 10 years. In the first round, 79,859 women were invited to participate in the MSP and 52,558 accepted (acceptance rate of 65.8%). Furthermore, 1,458 women who were not invited were referred to the screening for breast symptoms (pain, discharge, or mass). The total recall rate for biopsy was 8.1 per 100,000 women with a detection rate of 10.2 per 100,000 women. Finally, 4,730 women left the MSP after the first mammogram (abandonment rate of 9.0%) (Table 1).

Table 1. Characteristics of population invited to breast cancer screening in province of Modena

Characteristic	First round in 1996
No. of women invited	79,859
Total respondents	52,588
Spontaneous screening	1,458
Nonrespondents	20,498
Response rate (no. of invited respondents) (%)	65.8
Percentage no. of invited nonrespondents (%)	25.6
Total detection rate (×100,000)	10.2
Recall rate for biopsy (×100,000)	8.1
Rate of abandonment (%)	9.0

All of the women in this study were weighed, whereas heights were self-reported. BMI, defined as weight in kilograms divided by height in meters squared (kg/m^2), was calculated only for women with complete height and weight data. Based on the BMI, women were grouped into the weight categories recommended by the World Health Organization (WHO) [15]: underweight (BMI <18.5 kg/m^2), normalweight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Our study population was drawn from women who underwent mammography screening between July 1, 2004, and July 31, 2006, and were followed until December 31, 2010. Because only anthropometric data that are part of regular clinical records were collected, the approval of the local ethical committee was not required. During the study period, 71,612 women underwent screening mammography, 36,607 of whom were 55 to 69 years of age. All women were invited to participate in the study via an advertising campaign at the mammography screening site. Height and weight measurements were collected from all women who agreed to be weighed (15,702 women). We excluded women who had been diagnosed with another cancer before or during the enrollment period (n = 1,018). Therefore, the final study population consisted of 14,684 women (Figure 1).

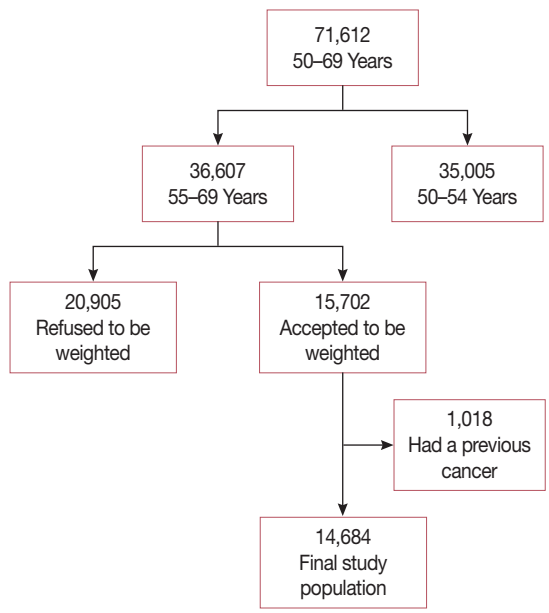

Figure 1. Flow-chart of the study.

http://dx.doi.org/10.4048/jbc.2016.19.3.283

Table 2. Characteristics of the final study population, subdivided by age range and body mass index

BMI (kg/m^2)	Age range (yr)			
	55–59 No. (%)	60–64 No. (%)	65–70 No. (%)	Total No. (%)
<18.5	30 (0.6)	22 (0.4)	27 (0.7)	79 (0.6)
18.5–24.9	2,518 (45.7)	1,980 (40.2)	1,685 (39.7)	6,183 (42.1)
25–29.9	2,013 (36.5)	1,976 (40.1)	1,773 (41.7)	5,762 (39.2)
≥30	949 (17.2)	949 (19.3)	762 (17.9)	2,660 (18.1)
Total	5,510 (37.5)	4,927 (33.6)	4,247 (28.9)	14,684 (100)

BMI = body mass index.

The characteristics of the final study population, subdivided by age range and BMI, are reported in Table 2. Among 14,684 women, 79 were underweight, 6,183 were normal-weight, 5,762 were overweight, and 2,660 were obese. Baseline characteristics regarding the remaining 20,905 women who were not weighed are lacking. However, considering a national prospective study from the Italian Institute of Health in which women aged 50 to 69 years were randomly interviewed about their physical condition, 57.8% were overweight or obese, as in our sample [16].

Statistical analysis

Cancer cases were identified by record linkage with the Modena Cancer Registry (MCR). All the patients within the age range of 55 to 69 years diagnosed with BC in the period 2004 to 2010 were selected from the MCR, which has operated since 1988 and collects all new cases of cancers occurring in residents of the Province of Modena, Italy. The Province of Modena, located in northern Italy, extends over 2,682 km^2 and has 47 municipalities. A cross-linkage between data from the MSP and MCR allowed the identification of cases with invasive or *in situ* BC diagnosed at the MSP between July 1, 2004, and December 31, 2010, with the last follow-up updated on December 31, 2012. All BC cases were identified as International Classification of Disease (ninth revision, code 174). Cases diagnosed on the basis of a death certificate only were excluded; only microscopically confirmed cases were included for analysis. For every case, data on histology, staging at presentation (based on the 2009 Union for International Cancer Control Tumor-Node-Metastasis classification) [17], and treatment were obtained from clinical records. All the events (local or distant recurrence, second breast or nonbreast tumors, and deaths from BC or from any other cause) that occurred among these women during the follow-up period were retrieved by experienced clinical documentation clerks with active follow-up strategies.

The chi-square test was used to determine differences in clinic-pathological features between the BMI groups and between cases diagnosed in the study and screen-detected tumors matched for age and calendar- period. We used a Poisson regression model to estimate relative risk (RR) and 95% confidence intervals (CIs) for overweight and obesity relative to normal BMI, adjusted for age and hormonal receptors. We believed that this model was suitable for a closed cohort like our population where a very low number of women migrate out of the Modena Province and the number lost to follow-up is negligible. Two distinct models were fitted, with BMI as a categorical variable or as a linear trend. Other variables, such as use of oral contraceptives or hormonal replacement therapy, age at menarche, parity, breastfeeding, or family history of BC were not evaluated in this model.

However, we subdivided BC cases according to selected clinicopathological characteristics obtained from the MCR database and we estimated the hazard ratio of BC incidence according to hormone receptor status between cases diagnosed in the study and screen-detected tumors matched for age and calendar-period. The Cox proportional hazards regression model was used in multivariate analysis to determine whether the identified risk factors independently influenced incidence of BC. The covariates selected were BMI, tumor size, nodal involvement, and stage (I vs. others). The normal-weight BMI group was used as the reference category to calculate the RR. Hazard ratios and 95% exact and mid-p CIs were calculated and the Wald method was used to test for significance.

The 5-year event-free survival (EFS) was defined as the time from diagnosis until the appearance of the first recurrence of BC or a second cancer. Survival was estimated by the Kaplan-Meier method, and any differences in survival were evaluated with a stratified log-rank test.

We conducted the analysis using STATA (8.0 SE version) statistical package (StataCorp LP, College Station, USA). Differences were considered statistically significant when the *p*-value was ≤0.05. All statistical tests were two-sided.

RESULTS

Incidence of breast cancer

In total, 14,684 women were eligible for analysis. The mean age at recruitment was 63±4.4 years and the mean BMI at baseline was 26.4±4.4 kg/m^2. The mean age at diagnosis was 63.5±10.5 years since the last cohort of women was entered into the MSP at 69 years of age in 2006; they were followed until the age of 74 years. The median time between the first mammogram and diagnosis of BC was 27 months (range, 0–73 months), considering both prevalent and interval can-

Table 3. Relative risk of breast cancer according to body mass index of 14,684 women

	Mean±SD	No. of BC	Population (%)	RR	95% CI	*p*-value
BMI (kg/m^2), categorical						
<18.5	16.2±1.3	0	79 (0.6)	0	-	-
18.5–24.9	22.6±2.2	139	6,183 (42.1)	1.0	-	-
25–29.9	27.2±1.4	149	5,762 (39.2)	1.17	0.92–1.47	0.180
≥30	33.5±3.2	78	2, 660 (18.1)	1.32	1.00–1.75	0.040
BMI, continuous*	-	-	-	1.21	1.05–1.40	0.008

BMI=body mass index; BC=breast cancer; RR=relative risk; CI=confidence interval.
*Linear trend.

cers. The average observation time of the cohort was 70.61 months. The total observation time was 86,442 person-years. During the 6-year follow-up period, 905 screen-detected cancers occurred (nonmelanoma skin cancers were excluded) in women aged 55 to 69 years who were not included in our study. Among women weighed during the study period, 366 cases of BC were registered, of which 308 were invasive BC and 58 were *in situ* BC. Among the 366 BC cases, 139 were in the normal-weight group, 149 in the overweight group, and 78 in the obese group. No BC cases were registered in the underweight group of women. The mean interval between the first mammogram and diagnosis of BC was significantly longer in the normal-weight patients (31 months) compared with overweight (25 months) and obese (28 months) women ($p=0.030$).

Table 3 shows the RR of BC according to BMI, adjusted for age. Compared with normal-weight women (RR=1), the RRs for overweight and obese women were 1.17 and 1.32, respectively (95% CIs, 0.92–1.47 and 1.00–1.75, respectively). When BMI was entered into the model as a continuous variable, the estimated RR associated with a linear trend for BMI was 1.21 (95% CI, 1.05–1.40).

Tumor characteristics

A comparison between 905 patients diagnosed by the MSP who were not included in our study and 366 patients diagnosed who were included in the study is shown in Table 4. Patients diagnosed within the study had an increased tumor size and were more frequently axillary node-positive.

The analysis of the tumor characteristics in relation to BMI (Table 5) showed that obese women had a higher percentage of larger tumors (27% of tumors were >2 cm) compared with overweight women (8.1%) and normal-weight women (10.7%) ($p=0.002$, obese vs. overweight and normal-weight women). Obese women also had higher percentages of node-positive cancers (38.5% of tumors were node-positive) compared with overweight women (21%) and normal-weight women (22.9%) ($p=0.040$, obese vs. overweight and normal-

Table 4. Comparison on histopathology characteristics between cases diagnosed in study population and all cases S-D aged 50–69 years diagnosed in period 2004–2006 in province of Modena

Characteristic	Cases by population in study (n=366) No. (%)	All cases S-D diagnosed in period 2004–2006 by MCR (n=905) No. (%)	*p*-value
Tumor diameter (mm)*	13±2	12±1	0.790
Missing value (%)	9.3	16.3	
T stage			0.029
Tis	57 (15.6)	195 (21.5)	
T1 mic-a-b	124 (33.9)	320 (35.4)	
T1c	131 (35.8)	301 (33.3)	
T2	44 (12.0)	65 (7.2)	
T3–T4	4 (1.1)	10 (1.1)	
TX	6 (1.6)	14 (1.5)	
N stage			0.010
N0	254 (69.4)	651 (71.9)	
N1	71 (19.4)	125 (13.8)	
>N1	22 (6.0)	45 (5.0)	
NX	19 (5.2)	84 (9.3)	
M staging			0.730
M0	362 (98.9)	896 (99.1)	
M1	4 (1.1)	8 (0.9)	
Grading			0.750
I	38 (10.4)	117 (12.9)	
II	179 (48.9)	409 (45.2)	
III	134 (36.6)	312 (34.5)	
Unknown	15 (4.1)	67 (7.4)	
Ki-67 (%)			0.130
≤20	242 (66.1)	568 (62.8)	
>20	67 (18.3)	152 (16.8)	
Unknown	57 (15.6)	185 (20.4)	
Hormonal status			0.140
ER+/PR+	272 (73.2)	650 (71.8)	
ER+/PR–	14 (4.1)	53 (5.9)	
ER–/PR+	2 (0.5)	6 (0.7)	
ER–/PR–	32 (9.3)	54 (6.0)	
Unknown	46 (12.8)	142 (15.7)	

Data are presented as number (%).
S-D=screen-detected; MCR=Modena Cancer Registry; ER=estrogen receptor; PR=progesterone receptor.
*Mean±SD.

http://dx.doi.org/10.4048/jbc.2016.19.3.283

Table 5. Histopathology characteristics of 366 breast cancers

Characteristic	BMI (kg/m²)			*p*-value
	18.5–24.9 No. (%)	25–29.9 No. (%)	≥30 No. (%)	
Tumor diameter (mm)*	13±2	11±1	17±3	0.002
T stage				0.002
Tis	25 (17.9)	23 (15.5)	9 (11.5)	
T1 mic-a-b	45 (32.1)	62 (42.0)	17 (21.8)	
T1c	50 (35.7)	50 (33.8)	31 (39.7)	
T2	13 (9.3)	12 (8.1)	19 (24.4)	
T3–T4	2 (1.4)	0	2 (2.6)	
TX	5 (3.6)	1 (0.7)	0	
N stage†				0.040
N0	97 (69.3)	111 (75.0)	46 (59.0)	
N1	26 (18.6)	22 (14.9)	23 (29.5)	
>N1	6 (4.3)	9 (6.1)	7 (9.0)	
NX	11 (7.9)	6 (4.1)	2 (2.6)	
M stage				0.210
M0	137 (98.0)	148 (100)	77 (99)	
M1	3 (1.4)	0	1 (0.3)	
Grading				0.480
I	17 (12.3)	15 (10.1)	6 (7.7)	
II	66 (47.8)	75 (50.7)	38 (48.7)	
III	47 (34.1)	54 (36.5)	33 (42.3)	
Unknown	8 (5.8)	4 (2.7)	1 (1.3)	
Ki-67 (%)				0.130
≤20	96 (68.6)	95 (64.2)	51 (65.4)	
>20	19 (13.6)	28 (18.9)	20 (25.6)	
Unknown	25 (17.9)	25 (16.9)	7 (9.0)	
Hormonal status				0.950
ER+/PR+	103 (73.6)	107 (72.3)	62 (79.5)	
ER+/PR–	6 (4.3)	6 (4.1)	2 (2.6)	
ER–/PR+	1 (0.7)	1 (0.7)	0	
ER–/PR–	11 (7.9)	14 (9.5)	7 (9.0)	
Unknown	19 (13.6)	20 (13.5)	7 (9.0)	

Data are presented as number (%).
BMI=body mass index; ER=estrogen receptor; PR=progesterone receptor.
*Mean±SD (34 missing value);†N0=N0+N0i; N1=N1+N1mic+N1a; >N1=N2+N2a+N3.

Table 6. Multivariate logistic model on 366 breast cancer cases

BMI category (kg/m²)	HR	95% CI	*p*-value
Overweight (25–29.9)			
Receptor status			
ER+/PR+	Ref.	-	-
Other receptor status*	1.09	0.54–2.18	0.798
Age at diagnosis			
59±5.3 yr (normal weight)	Ref.	-	-
62±4.6 yr	1.02	0.96–1.07	0.529
Stage			
I	Ref.	-	-
II	0.65	0.35–1.20	0.175
III	0.75	0.28–2.00	0.567
Obese ≥30			
Receptor status			
ER+/PR+	Ref.	-	-
Other receptor status*	0.91	0.38–2.19	0.840
Age at diagnosis			
59±5.3 yr (normal weight)	Ref.	-	-
63±5.2 yr	1.04	0.97–1.11	0.185
Stage			
I	Ref.	-	-
II	2.79	1.42–5.49	0.003
III	2.33	0.81–6.71	0.115

BMI=body mass index; HR=hazard ratio; CI=confidence interval; ER=estrogen receptor; PR=progesterone receptor; Ref.=reference category.
*Other receptor status=ER+/PR–; ER–/PR+; ER–/PR–.

weight women). Data on human epidermal growth factor receptor 2 status were lacking in most cases because at that time it was not routinely tested.

Regarding hormone receptor status, all BMI groups had a higher percentage of estrogen receptor (ER) positive and progesterone receptor (PR) positive tumors (73.6% in normal-weight, 72.3% in overweight, and 79.5% in obese women) compared with the other three tumor receptor categories, but the results were not statistically significant. Particularly, a Poisson regression analysis between different categories of BMI and hormonal receptor status showed that obesity represented a statistically significant risk factor for hormonal receptor-positive BC compared with hormonal receptor-negative BC in which no differences were seen among the three groups of patients (data not shown). A multivariate analysis evaluating the normal-weight women as the reference category and stage and hormonal receptor status as covariates showed that obese women more frequently had an advanced stage (higher than stage I) of disease ($p=0.003$) (Table 6).

Tumor treatments

Among 366 BC cases diagnosed in the study, 102 patients (27.9%) were treated with chemotherapy and 265 (72.1%) with hormonal treatment. A statistically nonsignificant trend of increased use of chemotherapy was shown for obese patients compared with normal and overweight patients (35.9% vs. 25% and 26.3%, respectively, $p=0.237$), consistent with the more advanced stage of disease in this group of women. No statistically significant differences were seen for hormonal treatment, although a trend in favor of obese women was shown (78.2% vs. 67.9% for normal-weight and 73.6% for overweight women, respectively, $p=0.300$). Among the different chemotherapy regimens used, anthracycline-based treatments represented the most frequently adopted regimen (52.0%), followed by taxane-based regimens (32.5%), cyclophosphamide/methotrexate/fluorouracil (9.7%), and others (5.8%). This distribution of regimens reflects the era in which anthracycline represented the milestone of BC chemotherapy.

Table 7. Distribution of second events in relation to body mass index of patients at diagnosis of first breast cancer

Events	BMI (kg/m^2)			*p*-value
	18.5–24.9 (n=140) No. (%)	25–29.9 (n=148) No. (%)	≥30 (n=78) No. (%)	
Recurrence	3 (2.1)	4 (2.7)	4 (5.1)	0.440
Second breast cancer	10 (7.2)	4 (2.7)	2 (2.5)	0.120
Other second malignancies	2 (1.4)	9 (6.0)	8 (10.2)	0.016
Total events	15 (10.8)	17 (11.4)	14 (17.9)	0.032

BMI=body mass index.

Finally, among hormonal treatments, aromatase inhibitors were the most used drugs (74.3%), with the remaining therapy consisting of tamoxifen (25.7%).

Event-free survival

After 104 months from the first BC diagnosis, with a median follow-up period of 65 months (range, 2–104 months), we observed 46 events, including 11 BC recurrences (local and distant), 16 second BC tumors, and 19 other second malignancies. We observed four BC recurrences in obese women, four in overweight women, and three in normal-weight women, without statistical significance ($p=0.440$). No differences were seen for second BC tumors, but a significantly higher rate of other second malignancies occurred in obese patients, who developed two colon, one endometrium, one pancreas, two lung, one melanoma, and one hematological (leukemia) malignancy. In total, the rate of events was higher in obese than in non-obese women (17.9% of obese BC patients developed events, $p=0.032$) (Table 7).

The 5-year EFS was 80.0%, 89.0%, and 89.0% among the obese, overweight, and normal-weight women, respectively ($p=0.200$) (Figure 2).

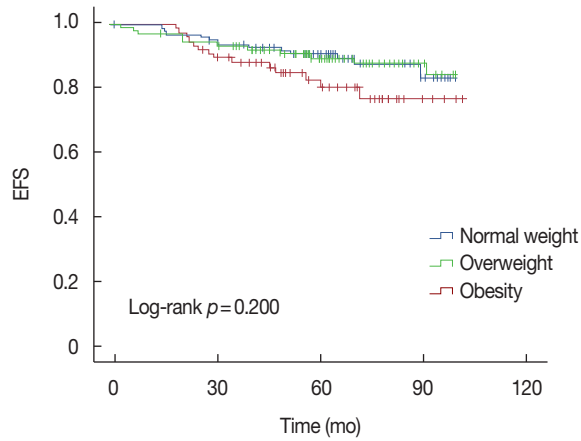

Figure 2. Five-year event-free survival (EFS) among obese, overweight and normal-weight women. EFS for normal weight (blue line) and overweight (green line) patients was equal to 89.0%. Patients with obesity (red line) had and EFS of 80.0% ($p=0.2$).

DISCUSSION

We examined BC incidence, recurrence, and second tumor development in relation to BMI in our study population. In this large cohort study of women aged 55 to 69 years participating in the MSP, obese women showed an increased risk for BC compared with normal-weight and overweight women This study also confirms that BC tumors in obese women are likely to be larger and more frequently node-positive than those in other groups of patients. Furthermore, obese women develop more second events, particularly second non-BC tumors. Finally, this study shows an unfavorable prognosis of obese patients in terms of developing BC recurrences and other tumors at 5 years of follow-up, even though the differences were not significant in our study.

The association between measures of body size and risk of BC has been confirmed in numerous studies [2-4,18]. In general, obesity has been found to be positively associated with a higher risk and a poorer prognosis of postmenopausal BC [12,19]. To establish with acceptable certainty that all participants were postmenopausal, we considered in this study only women aged 55 to 69 years.

Our findings are compatible with those of previous studies [1-4,12-14,18,19], where a positive association between BMI and risk of postmenopausal BC was seen. Indeed, the RR for postmenopausal BC among obese women was significantly higher than that for normal-weight women.

Moreover, we found that obese women were more likely to present with a larger tumor size compared with normal-weight women, and the difference was statistically significant. The present finding is consistent with other study results showing an association of obesity with tumors with poor prognostic characteristics; in fact, all of those studies found that an increased BMI or other measures of adiposity were significantly associated with an increased risk of cancer stage being higher than stage II (according to the American Joint Committee on Cancer staging system) and with an increased frequency of grade III tumors [20-22].

Several studies have examined whether the risk of postmenopausal BC associated with obesity is heterogeneous according to ER/PR status [23-25]. In our study, we observed an increased risk of ER and PR positive tumors in all BMI categories examined. Other data suggest an increase in receptor-positive BC in obese women [23-25], and the current study may show a trend in that direction, but it was not statistically

http://dx.doi.org/10.4048/jbc.2016.19.3.283

significant, perhaps owing to a relatively small sample size or relatively short duration of follow-up.

The more advanced stage at diagnosis and the more biologically aggressive tumors can explain why obese BC patients have a worse prognosis, since they are more likely to develop local and distant recurrences.

We demonstrated that obesity was associated with an increased risk of a second event. Particularly, a statistically significant association was found for second non-BC tumors. Because a second BC tumor represents the most frequent tumor occurring after primary BC [26,27] in all patients affected, no differences were seen between different groups of patients for this event probably because of the small number of cases. Indeed, colorectal, endometrial, and pancreatic cancers, which are more represented in the obese patient group, are considered as related to BMI, as demonstrated in a prospective cohort study of over 1 million women [14]. In this study, Reeves et al. [14] showed an association between increased BMI and an increased incidence of endometrial cancer (trend in RR per 10 units, 2.89; 95% CI, 2.62–3.18), pancreatic cancer (1.24, 1.03–1.48), and colorectal cancer (1.61, 1.05–2.48) in premenopausal women.

The 5-year EFS curve shows only a negative trend for obese patients without reaching statistical significance, probably because many second events occurred in the last 3 years of follow-up. Moreover, there are many late recurrences of receptor-positive BC and a 5-year follow-up may be too short to accurately determine the overall relapse rate, which could in turn ultimately affect the survival curves. A further explanation is that the lack of increased risk of BC recurrence and a second BC could have been influenced by the hormonal adjuvant treatment received by patients because the majority had a hormone-dependent BC. In any case, our findings are broadly consistent with those of previous studies showing that patients with BC who are obese demonstrate a poor prognosis [8,10-12,14]. Particularly, in a systematic review of numerous studies collectively incorporating more than 29,000 women with invasive BC, Chlebowski et al. [9] showed a statistically significant increased risk of disease recurrence and mortality in obese women compared with lean women, with hazard ratios ranging from 1.3 to well over 2.

The primary strength of this study is the prospective design, which gave us the ability to examine, with adequate statistical power, the association between BMI and the risk of BC in postmenopausal women. To our knowledge, no previous study has examined the role of BMI in the incidence of BC in a large Italian cohort of postmenopausal women.

Moreover, our evaluation of the relationship between BMI and BC incidence in women participating in the MSP supports emerging considerations of screening program locations as one of the first possible settings for cancer prevention and education.

Finally, we note that our study was made possible and facilitated only by the existence of a population-based cancer registry in the area. Through the registry, we recognized all new cases of cancers in women aged 55 to 69 years and obtained information about their follow-up status. We consider a cancer registry an important tool for adequate monitoring of screening programs.

This study has several limitations. A weakness is that menopausal status was assessed based only on age criteria. Because we did not collect data on the menopausal status, we included only women aged 55 to 69 years in view of the fact that the median age at menopause in Europe ranges from 50.1 to 52.8 years [28]. Moreover, because the results are from a population of predominantly white middle-aged or elderly women, they may not be generalizable to other populations of interest.

However, considering that according to the MCR data, approximately 60% of BC arises in women aged 55 to 69 and 70% of these patients adhere to the MSP, our data could reflect approximately half of the BC population. Furthermore, no baseline characteristics were collected from women not entered into the study, which could represent a selection bias, although a comparison with the "Progressi delle Aziende Sanitarie per la Salute in Italia" study seems to correlate with our data regarding the percentage of overweight and obese women (57.8%) among the general population aged 50 to 69 years [16]. Younger or older women have to be better investigated to explore other risk factors and BMI conditions at that age. Another limitation is the potential for measurement error from self-reported height, although the correlation of self-reported height with measured height has been reported to be high, ranging from 0.80 to 0.95 [29,30].

Another limitation of the study is that body weight was measured only at the mammography examination and may not reflect the weight at diagnosis or recurrence, because patients may have lost or gained weight at that time. Moreover, the sample size of 366 women with BC is small for the outcome analysis.

Finally, because information on the potential confounders (e.g., reproductive and menstrual history and hormone replacement therapy use) was not available, it was not possible to calculate adjusted RRs.

In conclusion, despite the limitations described above, we observed a significantly higher risk of postmenopausal BC and a higher rate of second events in obese women in the Province of Modena.

Our findings support the evidence that obesity, however

measured, adversely affects the development of BC. Furthermore, obese women represent a group of patients at risk for other obesity-related cancers, such as colorectal, endometrial, and pancreatic cancer. Obesity is one of the few risk factors for BC that can be modified throughout life. Thus, a continuous surveillance of the effect of BMI on BC incidence and prognosis is needed. Finally, weight management should be an integral part of BC screening and prevention strategies.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

The collection of breast cancer data used in this study was supported by the Modena Cancer Registry. Moreover, the authors would like to acknowledge the staff of Mammographic Screening Centre of Modena for the precious contribution to the collection of study data.

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